SHOULD SCREENING FOR LUNG CANCER BE REVISITED?*

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Over the past 15 to 20 years, lung cancer has become the most prevalent form of malignancy in men and the second most common in women. In addition, it has also become the leading cause of cancer death in both men and women. Unfortunately, these statistics are unlikely to change in the near future even though the number of smokers in the United States has significantly decreased to 20% to 25% of the population.

In the management of lung cancer, surgical resection offers some possibility for cure, although most new patients are first seen when it is already too late to operate. Indeed, 5-year survival figures are consistently in the range of 10% to 12% even if they rise to 25% to 30% in those few individuals who can have complete resection of their tumors. The disease can, however, be cured in up to 70% of cases if surgically managed while still in its earliest stages (clinical stages Ia and Ib). Because of these better survival figures, it is tempting to assume that with lung cancer screening, tumors will be diagnosed at an earlier stage and cure rates will be higher. This seems even more likely if one considers that lung cancer should easily be identifiable on chest radiographs or by sputum cytology. In this context, it may be worth noting that tumors smaller than 2 cm are not necessarily early-stage neoplasms (up to 20% already have N2 status); on the other hand, some of these tumors can be slow growing so that 5-year survivals may not be an accurate way of reporting results.

The two methods traditionally used for early detection of lung cancer are standard chest radiographs and sputum cytologic examination. Chest radiographs can detect lung nodules of 0.8 to 1 cm in diameter, whereas sputum cytology will be "positive" in 30% to 40% of endobronchial lesions. Both techniques are inexpensive and excellent for individual cases. Three randomized studies[1-3] done in the 1970s and supported by research contracts from the National Institutes of Health have shown, however, that the death rate from lung cancer was not significantly different in patients who were actively screened than in patients who were not (3.2/1000 patients vs 3.0/1000 patients in the Mayo lung project[3]). Even if some of the methods used in those trials were criticized, their failure to show a significant reduction in cancer death rates was and still is considered strong evidence against screening. These techniques may also have some potential to be harmful through false positive radiographs (0%-10%/year), false positive cytologic reports (0%-1%/year), and chances of incorrect cancer diagnosis (0%-1%/year).[4]

More recently, these techniques have evolved to those of screening by low-dose helical computed tomography (CT) and use of specific biomarkers for lung cancer. The Early Lung Cancer Action Project (ELCAP)[5] notably looked at the usefulness of annual helical low-dose CT scanning in 1000 heavy smokers over the age of 60 years. Helical CT detected 233 individuals (23%) with noncalcified nodules, but in only 27 (12%) were the nodules malignant. Of these 27 patients, 16 are included in the current report by Altorki and associates,[6] which suggests that CT scan can detect lung cancer at an earlier stage than chest radiographs. This would appear obvious since CT scanning is much more sensitive to detect small nodules than standard radiographs. Whether these findings translate into actual improvements in lung cancer death rates (the most important end point in cancer screening) is unknown, not only because the number of patients in the CT group is small, but also because no long-term follow-up is given for this cohort. One should also note that 91% of patients in the CT group had adenocarcinoma, a ratio that does not reflect the true proportions of this tumor among all histologic types of lung cancer.

As shown by the original data from ELCAP,[5] one of the drawbacks of screening with low-dose helical CT is the number of detected nodules that are initially interpreted as being nonmalignant. If one was to keep the same ratio as reported by ELCAP, screening by CT would translate into finding approximately 220,000 presumably nonmalignant nodules in a screened population of 1,000,000. What will be done with these patients will largely be left to the judgment of individual physicians, although this judgment is likely to be influenced by the patient's anxiety or the physician's

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fear of being involved in legal actions if a malignant nodule is diagnosed too late. These are some of the reasons why I think that screening by CT should be reserved for very high-risk patients such as those heavy smokers (or former heavy smokers) with a personal or family history of any type of malignancy or with occupational exposure to known carcinogens. Indeed, the highest risk group for lung cancer is the group of patients with prior lung cancer (2%-5%/year). The problem of over diagnosis, that is, diagnosing a lung cancer that is unlikely to become life-threatening, is a nonissue because it has been repeatedly shown that most untreated lung cancers are likely to progress and cause death within 5 years of their diagnosis. In the three screening programs previously mentioned,[1-3] the 5-year survival of patients with screen-detected lung cancer who did not undergo surgery was below 10%.

Perhaps a more specific method of screening patients at risk for lung cancer is through the use of biomarkers applied to sputum specimens. In 1988, Tockman and associates[7] reported on two monoclonal antibodies (703D4 and 624H12) that were identified as biomarkers of lung cancer. When applied to the Johns Hopkins early lung cancer specimens, these antibodies together showed a sensitivity of 91% and a specificity of 88% for the diagnosis of lung cancer within 2 years. Since then, clinical trials to evaluate these biomarkers have been designed with the hypothesis that screening with immunostaining techniques will increase the percentage of detected stage I lung cancers at least 3-fold.[8] It is of interest to note that sputum for cytologic analysis is best obtained after saline aerosol induction and that microscopic workstations have already been developed to extract positive immunostained cells. It may soon be possible that chemo-preventive agents delivered by inhalation will be given to destroy such early tumors before they become invasive.

Because of major advances in these new technologies, lung cancer screening programs should be reopened, perhaps by combining the use of low-dose helical CT and immunostaining techniques. Initially, at least, eligibility for those programs should be restricted to very high-risk patients.

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